Sudden death (SD) in ventricular preexcitation (VP) syndrome, although rare,¹⁻³ arouses a great deal of interest because it often occurs in young, otherwise healthy individuals. In most cases, SD is the result of rapid ventricular response over the accessory pathway, which might be triggered by a primary atrial pathology or be secondary to atrioventricular (AV) reentrant tachycardia.²,⁴ When one considers that histological confirmation of accessory pathways may require expert preparation and scrutiny of thousands of sections, it is not surprising that pathology lags far behind clinical studies. Thus, previous reports on SD patients are anecdotal and often lack autopsy validation; likewise, no data are available on VP as a cause of SD in the young. The present study was undertaken to assess prevalence and clinicopathological features of VP in a series of young adults who died suddenly.

Methods
Since 1979, a clinicopathological prospective study of SD in children and young adults (≤35 years) has been ongoing in Northeastern Italy. All hearts from cases of SD are systematically assessed at the University of Padua. Distribution of various causes of SD has been previously reported.⁵ For inclusion in the study group, each patient fulfilled the following criteria: (1) ECG diagnosis of VP; (2) ≤35 years of age at time of death; (3) absence at autopsy of other cardiac and noncardiac causes of death; and (4) no evidence of drug or alcohol abuse on the postmortem toxicological examination.

Clinical history was reviewed, and particular attention was paid to previous symptoms or signs, electrophysiological investigation, and circumstances of death.

Wolff-Parkinson-White (WPW)-type VP was diagnosed by 12-lead ECG in the presence of short PR interval (≤0.12 s) and widening of the QRS complex (>120 ms) with slurred, slow rising onset of QRS (so-called Δ-wave). The site of AV connection was predicted according to ECG criteria of Arruda et al⁶ (ie, Δ-wave axis in the frontal leads and Δ-wave polarity in the precordial leads).

Lown-Ganong-Levine (LGL)-type VP or enhanced AV nodal conduction was diagnosed by 12-lead ECG in the presence of short PR interval (≤0.12 s) and normal QRS complex (≤120 ms).

Gross examination of the heart addressed weight, wall thickness, myocardium, endocardium, valves and coronary arteries, inflow and outflow tracts and great vessels.

Routine histology of the ordinary myocardium (stained with hematoxylin-eosin and Heidenhain trichrome) was performed on 8 transmural samples obtained in cross section from the left ventricle.
TABLE 1. Clinical Data in 10 Patients With VP

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex, Age, y</th>
<th>Symptoms</th>
<th>Circumstances of Death</th>
<th>Rhythm</th>
<th>HR, bpm</th>
<th>PR, s</th>
<th>Delta Wave (Δ)</th>
<th>Other Findings</th>
<th>Predicted Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M, 34</td>
<td>Syncope, palpitations</td>
<td>At rest (sleep)</td>
<td>Sinus</td>
<td>118</td>
<td>0.10</td>
<td>Δ+</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>M, 21</td>
<td>Syncope, palpitations</td>
<td>At rest (sleep)</td>
<td>Sinus</td>
<td>70</td>
<td>0.12</td>
<td>Δ+</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>3</td>
<td>M, 20</td>
<td>Palpitations</td>
<td>At rest</td>
<td>Sinus</td>
<td>70</td>
<td>0.08</td>
<td>Δ++</td>
<td>R&gt;s</td>
<td>Δ superior/intermediate</td>
</tr>
<tr>
<td>4</td>
<td>M, 19</td>
<td>...</td>
<td>At rest</td>
<td>Sinus</td>
<td>68</td>
<td>0.10</td>
<td>Δ++</td>
<td>r≤s</td>
<td>Δ superior</td>
</tr>
<tr>
<td>5</td>
<td>M, 24</td>
<td>...</td>
<td>At rest (sleep)</td>
<td>Sinus</td>
<td>87</td>
<td>0.12</td>
<td>Δ+</td>
<td>R≤s</td>
<td>Δ intermediate</td>
</tr>
<tr>
<td>6</td>
<td>M, 26</td>
<td>Palpitations</td>
<td>At rest (sleep)</td>
<td>Sinus</td>
<td>31</td>
<td>0.04</td>
<td>Δ++</td>
<td>R&gt;s</td>
<td>Δ superior</td>
</tr>
<tr>
<td>7</td>
<td>M, 22</td>
<td>...</td>
<td>At rest</td>
<td>Sinus</td>
<td>80</td>
<td>0.08</td>
<td>Δ+</td>
<td>R&gt;s</td>
<td>Δ intermediate</td>
</tr>
<tr>
<td>8</td>
<td>M, 26</td>
<td>Syncope, palpitations</td>
<td>At rest</td>
<td>Sinus</td>
<td>60</td>
<td>0.08</td>
<td>Δ+</td>
<td>r≤s</td>
<td>Δ intermediate</td>
</tr>
<tr>
<td>9</td>
<td>M, 9</td>
<td>...</td>
<td>At rest</td>
<td>Sinus</td>
<td>70</td>
<td>0.06</td>
<td>Δ++</td>
<td>R&gt;s</td>
<td>Δ superior</td>
</tr>
<tr>
<td>10</td>
<td>M, 35</td>
<td>Palpitations</td>
<td>At rest</td>
<td>Sinus</td>
<td>70</td>
<td>0.10</td>
<td>Δ++</td>
<td>R&gt;s</td>
<td>Δ superior</td>
</tr>
</tbody>
</table>

Δ+ indicates slight positive; Δ++, positive; and Δ, delta wave axis on frontal leads.

Results

Clinical Data

The 12-lead ECG tracing was available in 93 of 273 cardiovascular SDs (34%), and 10 patients had ECG-documented VP (3.6% of the overall SD population and 10.5% of SDs with available ECG). Six percent of all SDs remained unexplained even after careful gross and histological examination.

VP patients were male (mean age, 24±7 years; age range, 9 to 35 years). Six patients (60%) had warning symptoms that consisted of palpitations; these symptoms were associated with syncope in 3 of the 6. The remaining 4 patients had an incidental ECG diagnosis at military service preenrollment screening (n=2), preparticipation screening for sport activity (n=1), and checkup before surgical procedure (n=1). SD occurred at rest in all but 1; 4 died during night sleep.

The 12-lead ECG tracing indicated WPW-type VP in 8 patients and enhanced AV conduction (LGL type) in 2. In the former, Δ-wave morphology suggested left lateral AV pathways in 6 (75%; posterolateral in 3 and lateral in 3), and right AV accessory pathways in 2 (posterolateral and lateral, 1 each); in 1 patient (patient 10), the 12-lead ECG tracing intermittently showed Δ-wave pattern (left lateral) or a normal QRS pattern without VP (Table 1).
Recurrent episodes of AV-reentrant tachycardia were reported in 5 patients (patients 2, 3, 6, 8, and 9). Electrophysiological study was undertaken only in 2 patients. Data for patient 1 have been previously reported. In patient 9, who presented with right lateral WPW-type VP, transesophageal study revealed a preexcited RR interval of 240 ms; the patient refused catheter ablation and died 3 years after the last examination. None of the patients had an ECG tracing at the time of cardiac arrest.

Pathological Data

Gross Examination
Heart weight (360±90 g) and left ventricular (12.5±1.0 mm), right ventricular (4±0.5 mm), and interventricular septal (12.5±1.5 mm) thicknesses were normal. Origin and course of the coronary arteries were regular in the absence of obstructive coronary artery disease. AV and semilunar valves were normal in all but patient 6, who presented with mitral valve prolapse. Patient 9 had previous surgical closure of patent ductus arteriosus.

Ordinary Myocardium Histology
No patient exhibited inflammatory infiltrates, myocytes necrosis or disarray, interstitial or replacement-type fibrosis, or fatty infiltration of the ventricular myocardium. Intramural small vessels were normal.

Focal, active myocarditis, which consisted of patchy inflammatory infiltrate with myocyte necrosis, occurred in 4 (50%) patients with WPW-type VP and was confined to the atrial myocardium. Inflammatory cell foci were multiple and bilateral and involved the myocardium around the pulmonary vein orifices in 2 cases, either close to (n=2) or far away from (n=2) the atrial ending of the accessory fascicle, but never did these foci affect the fascicle or conducting tissue (sinus node and AV junction). According to immunohistochemical findings, the inflammatory infiltrate was polymorphous in 1 (Figure 1) and lymphocytic (mostly activated T-lymphocytes, CD43 and CD45RO positive) (Figure 2) in 3 cases.

Control hearts did not show macroscopic or histological abnormalities; in particular, evidence of atrial myocarditis was never found.

Conduction System Investigation

LGL Syndrome
The sinus node structure was normal in both cases. Congenital AV nodal hypoplasia in patient 1 and right-sided atrio-Hisian tract in patient 2 were found. The latter was in a conspicuous atrial fascicle of ordinary and transitional myocardium and bypassed a morphologically normal AV node to anastomose distally with the common His bundle (the so-called James or Paladino fascicle).

WPW Syndrome
Sinus and AV nodal in addition to common His bundle and bundle branch anatomy was normal in all cases but 1 (patient 3), in whom the left bundle branch divided early in 2 parts, 1 subendocardial and 1 intramural septal, whereas the proximal right bundle branch insulated a cluster of ordinary myocytes to delineate a circuit. By serial histological sectional study of

Figure 1. Thirty-five-year-old man with a history of palpitations who died suddenly at rest with Δ-wave morphology on ECG suggestive for left posterolateral pathway location (case No. 10). A, Serial histological section of left lateral AV ring at level of posterior leaflet of mitral valve, showing 140-μm thick accessory fascicle (arrow) joining atrial and ventricular myocardium, very close to endocardium (Heidenhain trichrome ×8). B, Close-up of same showing partial replacement by fibrous tissue of ordinary myocardium of accessory pathway (Heidenhain trichrome ×24). C, Polymorphous inflammatory infiltrate associated with myocyte necrosis in atrial myocardium (hematoxylin-eosin ×160).

the septal and lateral AV junctions, 10 accessory AV pathways were found, which were located as expected by Δ-wave morphology on surface ECG in the left lateral ring in 7 (Figure 1) (double accessory pathways in patient 5) and right posterolateral ring in 2 (Figure 2); 1 of the latter was associated with a septal accessory AV pathway because of a gap in the fibrous septal annulus, which accounts for a mild Ebstein anomaly. (See Table 2.) These accessory AV pathways were all composed of ordinary myocardium, which accounts for the continuity between atria and ventricles. In the 2 hearts with right-sided connections, the accessory bundle typically crossed the AV groove at the point at which the fibrous annulus showed a gap. In contrast, left-sided AV connections always occurred in the presence of a well-formed fibrous annulus. Lateral AV accessory pathways showed a mean thickness of 310±190 μm, a mean distance from the endocardium of 750±530 μm, and a mean distance from the epicardium of 7610±1420 μm. Moreover, left lateral AV accessory pathways had a mean distance from the coronary sinus of 4430±1570 μm. (See Table 2.)
By comparing left-sided and right-sided accessory pathways, we found a significantly greater distance only from the epicardium of the former (8028 ± 1290 versus 6160 ± 791 μm; \( P = 0.04 \)). No difference was observed as far as thickness (247 ± 52 versus 530 ± 170 μm; \( P = \text{NS} \)) and distance from the endocardium (814 ± 582 versus 530 ± 325 μm; \( P = \text{NS} \)).

Curiously, the lateral bypass tract showed a vertical course in 5 cases (all left sided), whereas this tract presented an irregular and sinuous horizontal course in the remaining 4 cases (2 left-sided and 2 right-sided accessory AV pathways). In the patient with intermittent VP (patient 10), the myocardium of the accessory pathway was partially replaced by fibrous tissue at the ventricular end, at which only scattered residual muscular fibers were visible (Figure 1).

**Discussion**

**Present Study**

A 3.6% prevalence of VP in our series of young SD victims has been found. The fatal event was not preceded by warning symptoms in 40% of patients, and death almost invariably occurred at rest, often during sleep. Thus, occurrence of death was relatively unpredictable. As far as morphological findings, a left accessory pathway was the most frequent substrate; it consisted of a very thin muscular structure with a mean thickness of 310 μm located close to the endocardium. Surprisingly enough, ordinary myocardium histology revealed isolated acute atrial myocarditis in 50% of the patients, which was never detected in any control heart.

**VP and SD in Young People**

Estimated prevalence of WPW VP is 0.1 to 3.1 cases per 100010–12 and the overall risk of SD is low, reportedly occurring at a rate of ≤0.6% per year.1–3 No systematic data are available on prevalence of VP among SDs in the young,13–16 and our figures are probably underestimated, given that the conditio sine qua non for diagnosis was the availability of ECG tracing, a criterion fulfilled in only one third of cases. Notably, the 6% of SDs that remained unexplained after postmortem examination were in patients for whom no ECG tracing was done, which thus raises the suspicion of either hidden conduction-system abnormalities or nonstructural diseases. Likewise, by obtaining an ECG in nearly 50% of 57 apparently normal hearts referred for investigation of SD, Davies17 was able to diagnose VP in 7, in which subsequent study revealed accessory AV pathways.

**Anatomic Substrates of VP**

Accessory AV connections predisposing to VP may be “direct,” which are connections located outside the specialized AV junction that directly connect the atrial and ventricular myocardium (Kent fascicle) or “mediated,” which in...
Table 2. Pathological Data in Patients With WPW-Type VP

<table>
<thead>
<tr>
<th>No.</th>
<th>Type of Anomaly</th>
<th>Site</th>
<th>Diameter, ( \mu m )</th>
<th>Distance From Endocardium, ( \mu m )</th>
<th>Distance From Epicardium, ( \mu m )</th>
<th>Distance From Coronary Sinus, ( \mu m )</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral left AV ring</td>
<td>50</td>
<td>1400</td>
<td>6800</td>
<td>3600</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral right AV ring</td>
<td>360</td>
<td>760</td>
<td>6720</td>
<td>...</td>
<td>Lymphocytic atrial myocarditis</td>
</tr>
<tr>
<td>5</td>
<td>Double AV accessory pathways (ordinary myocardium)</td>
<td>a, Lateral left AV ring</td>
<td>440</td>
<td>380</td>
<td>8800</td>
<td>6000</td>
<td>Lymphocytic atrial myocarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b, Lateral left AV ring</td>
<td>300</td>
<td>360</td>
<td>7800</td>
<td>6000</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral left AV ring</td>
<td>140</td>
<td>540</td>
<td>9200</td>
<td>6000</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>7</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral left AV ring</td>
<td>360</td>
<td>320</td>
<td>9600</td>
<td>2400</td>
<td>...</td>
</tr>
<tr>
<td>8</td>
<td>Double AV accessory pathways (ordinary myocardium)</td>
<td>a, Posterolateral right AV ring</td>
<td>700</td>
<td>300</td>
<td>5600</td>
<td>...</td>
<td>Lymphocytic atrial myocarditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b, Septal AV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral left AV ring</td>
<td>300</td>
<td>1800</td>
<td>6000</td>
<td>4240</td>
<td>Previous closure PDA</td>
</tr>
<tr>
<td>10</td>
<td>AV accessory pathway (ordinary myocardium)</td>
<td>Posterolateral left AV ring</td>
<td>140</td>
<td>900</td>
<td>8000</td>
<td>2800</td>
<td>Accessory pathway fibrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polymorphic atrial myocarditis</td>
</tr>
</tbody>
</table>

PDA indicates patent ductus arteriosus.

Volve the specialized AV junction and either connect the septal atrial myocardium with the His bundle (James or Brechenmacher fibers) or the Tawarian system with the ventricular myocardium (Mahaim fibers).18,19

A rare condition that promotes early ventricular excitation is the so-called enhanced AV conduction or LGL syndrome.20,21 The impulse runs very quickly through the His bundle, with a short PR interval and a normal QRS complex. Two histological backgrounds in our series explained the missed delay at the AV node level. One is a congenitally hypoplastic AV node, which created a lessened bulk of specialized tissue to delay impulse transmission from atria to ventricles.8 The second is presence of an atrio-Hisian bundle that bypasses the AV node and transmits the activation signal directly to the His bundle.22,23 In both substrates, the onset of atrial fibrillation may precipitate ventricular fibrillation as it occurs in the WPW syndrome.

In WPW syndrome, an aberrant myocardial fascicle joins the atria to the ventricles beyond the specialized AV junction.23–26 This fascicle usually is located in the lateral rings and consists of a thin muscular segment that does not possess decremental conduction properties7 and may serve not only as bypass tract for VP but also as a limb for an AV reentry circuit, which accounts for a reciprocating supraventricular tachycardia. Impedance mismatch between the tiny anomalous fibers and the ventricular muscle bulk in addition to partial replacement of the accessory fascicle by fibrous tissue, as in 1 of our cases, might explain intermittent impaired antegrade conduction.27 Moreover, the accessory fascicle along the AV sulcus was always located close to the endocardium; size and site are such that Kent’s bundle is easily amenable to endocardial transcatheter ablation, the current procedure to reestablish AV electrical connection through the His bundle.28

Different sets of criteria for the localization of accessory pathways have been proposed on the basis of polarity of the QRS complex on various ECG leads. The present study confirms that the 12-lead ECG can be a good indicator of the site of accessory AV connection when the criteria of Arruda et al are applied.6

Pathophysiology of SD in VP

Cardiac arrest is believed to be related to the occurrence of atrial fibrillation,2 which may convert into ventricular fibrillation if the refractory period of the accessory pathway is short. The clinical profile of patients with WPW syndrome at risk of SD comes from the examination of those resuscitated from ventricular fibrillation. When compared with WPW patients without, those with ventricular fibrillation show a higher prevalence of both AV reentrant tachycardia and atrial fibrillation and are more likely to have multiple accessory AV pathways.29 Moreover, the shortest RR interval between the preexcited beats is <250 ms, as a result of rapid ventricular response over the accessory pathway. This feature, which was present in the only patient who underwent transesophageal study in our series, is considered the most important risk factor for the development of ventricular fibrillation. A patient with Ebstein’s anomaly or other concomitant heart disease is probably also at greater risk for ventricular fibrillation. Although patients with ventricular fibrillation or atrial fibrillation no doubt merit full electrophysiological investigation and interventional therapy, considerable controversy
still exists regarding the need for prophylactic treatment in asymptomatic individuals in whom the disease has been diagnosed by chance.86 However, these subjects have a small but definite risk of experiencing cardiac arrest as first manifestation of the disease, given that it occurred in half of our cases.

**Isolated Atrial Myocarditis as a Substrate of Paroxysmal Atrial Fibrillation**

Atrial fibrillation is reported in 20% to 30% of patients with WPW syndrome31 and may be accounted for by primary atrial pathology or be secondary to AV reentrant tachycardia. Typically, the electrophysiologic mechanism of atrial fibrillation consists of multiple migratory reentrant wave fronts of activation in both atria. This represents the rationale for curative therapy by surgical ablation or catheter-mediated ablation lines.32 Recently it has been suggested that, in a subset of young patients without structural heart disease, atrial fibrillation may be initiated by a focal rapidly firing source of activity.87 In this setting, abnormal automaticity or triggered activity is the most likely mechanism. The anatomic substrate of electrical atrial instability is difficult to investigate in vivo, because it requires either a surgical or, even rarer, an atrial biopsy approach. In the present fatal WPW cases, a 50% incidence of isolated atrial myocarditis was found. This finding, despite the absence of a final ECG tracing, supports the hypothesis that atrial inflammatory foci may act as a trigger of paroxysmal atrial fibrillation, which in turn precipitates SD due to very rapid ventricular conduction. Recent data suggest that lone paroxysmal atrial fibrillation may be due to isolated atrial myocarditis. In a series of 12 patients with drug-refractory paroxysmal atrial fibrillation studied by atrial endomyocardial biopsy, Frustaci et al34 found isolated atrial lymphocytic myocarditis in 66% of cases. The cause-effect relationship between myocarditis and atrial fibrillation was further supported by the absence of atrial fibrillation recurrence in patients treated with steroids during a mean follow-up of 12 months. More recently, Maixent et al35 demonstrated the presence of circulating autoantibodies against myosin heavy chain in 60% of patients with idiopathic paroxysmal atrial fibrillation, which raises the possibility of an autoimmune process. Moreover, Rossì86 looked at a small series of patients with atrial flutter or fibrillation and found striking right atrial inflammatory changes in 5 of 8 cases. Notably, the possibility of an isolated arrhythmogenic atrial myocarditis was put forward by Fromer et al,37 who studied 2 cases with drug-refractory ectopic atrial tachycardia; surgically resected atrial tissue showed focal myocarditis in the absence of concomitant ventricular abnormalities at endomyocardial biopsy associated with a minor elevation of antibodies against echovirus in 1 case. However, due to the intrinsic limitations of a postmortem study of formalin-fixed specimens and the inherent lack of feasibility of molecular biology investigation, the cause of the atrial inflammation remains intriguing.

In summary, 40% of young SD victims with VP experienced cardiac arrest as the first manifestation of the disease. In such patients, isolated atrial myocarditis may act as a trigger of paroxysmal atrial fibrillation leading to SD. This may account for the unpredictability of atrial fibrillation onset and difficulty on risk stratification.

**Acknowledgments**

This study was supported by Veneto Region, Venice, Italy and Murst, Rome, Italy. We thank Alessandra Dubrovich, Agostino Leonin, Mauro Pagetta, and Anna Saracino for the excellent technical support and Chiara Carturan for editorial assistance. The support of Fondazione Cassa di Risparmio di Padova e Rovigo is also acknowledged.

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Ventricular Preexcitation in Children and Young Adults: Atrial Myocarditis as a Possible Trigger of Sudden Death
Cristina Basso, Domenico Corrado, Lino Rossi and Gaetano Thiene

Circulation. 2001;103:269-275
doi: 10.1161/01.CIR.103.2.269

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